CAPSAICIN

CASRN: 404-86-4

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Human Health Effects:

Human Toxicity Excerpts:

THERE HAVE BEEN DESCRIPTIONS OF SEVERE CHRONIC BRONCHITIS, CAUSED BY PAPRIKA, LEADING TO BRONCHIECTASIS. WHILE FEW WORKERS ARE EXPOSED, DISABILITY...HAS BEEN SERIOUS. BOTANISTS HAVE DEVELOPED A KIND OF PEPPER PLANT CONTAINING LESS OF...TOXIC MATERIAL (CAPSAICIN), THEREBY CONTROLLING PROBLEM.
[Hamilton, A., and H. L. Hardy. Industrial Toxicology. 3rd ed. Acton, Mass.: Publishing Sciences Group, Inc., 1974. 461]**PEER REVIEWED**

There is some concern that capsaicin may be potentially neurotoxic, although ... clinical studies with topical capsaicin have not shown this to occur. Capsaicin is thought to be capable of elevating the heat pain threshold in the treated skin areas, especially in patients with diabetic neuropathy; these patients often already have an elevated threshold for heat and pain.
[USP Convention. USPDI-Drug Information for the Health Care Professional. 14th ed. Volume I. Rockville, MD: United States Pharmacopeial Convention, Inc., 1994. (Plus Updates). 710]**PEER REVIEWED**

Contact with products containing capsaicin produces local irritation and lacrimation. The use of dried red chili peppers (Capsicum annuum cultivar) caused severe burning of the fingertips of a man who earlier had sustained abrasions of the fingers. The name "Hunan hand" was given to this syndrome, which is caused by the volatile oils activating dermal pain fibers.
[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988. 1239] **PEER REVIEWED**

... /The/ irritating effect on the eyes has been utilized in pressurized dog repellent sprays which incorporate capsaicin. One boy accidentally had his eyes sprayed with this material. His eyes immediately smarted, teared, and became red, but were normal by the next day. Treatment had consisted only of irrigating with water, then mineral oil.
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986. 176]**PEER REVIEWED**

Skin, Eye and Respiratory Irritations:

Contact with products containing capsaicin produces local irritation and lacrimation.
[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988. 1239] **PEER REVIEWED**

Drug Warnings:

A mild to moderate burning sensation is experienced following application and, in some patients, can be pronounced enough to require discontinuation of treatment.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994. 148]**PEER REVIEWED**

/Capsaicin must be prevented/ from entering the eyes, open lesions, or mucous membranes.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994. 148]**PEER REVIEWED**

Patients may experience a warm, stinging, or burning sensation at the site of application, especially during the initial few days of use. Although this sensation frequently disappears after the first several days of treatment, it may persist for 2 to 4 weeks or longer. This effect is related to the initial excitatory effect of capsaicin on the C fibers and their release of substance P. The burning usually decreases in frequency and intensity with the continued administration of capsaicin. However, application schedules of capsaicin of less than 3 or 4 times daily may prolong the burning sensation while not providing optimum pain relief. Environmental factors, such as heat or humidity; wrappings, such as clothing or bandages; bathing in warm water; or sweating may intensify the sensation. The incidence of the burning sensation has been variable in difference studies. This may be related to the etiology and pathogenesis of the pain syndrome in different persons. For example, patients with arthritis generally experience less intense burning than do patients with peripheral neuropathies.
[USP Convention. USPDI-Drug Information for the Health Care Professional. 14th ed. Volume I. Rockville, MD: United States Pharmacopeial Convention, Inc., 1994. (Plus Updates). 710]**PEER REVIEWED**

If using capsaicin for treatment of neuralgia due to herpes zoster, /do/ not apply medicine until after zoster sores have healed.
[USP Convention. USPDI-Drug Information for the Health Care Professional. 14th ed. Volume I. Rockville, MD: United States Pharmacopeial Convention, Inc., 1994. (Plus Updates). 711]**PEER REVIEWED**

Minimum Fatal Dose Level:

3(?). 3= MODERATELY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 0.5-5 G/KG, BETWEEN 1 OZ & 1 PINT (OR 1 LB) FOR 70 KG PERSON. /CAPSICUM/
[Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976.,p. II-145]
PEER REVIEWED

Emergency Medical Treatment:

Emergency Medical Treatment:

EMT Copyright Disclaimer:

The following Overview, *** PLANTS-CAPSAICIN ***, is relevant for this HSDB record chemical.

Life Support:

- This overview assumes that basic life support measures have been instituted.

Clinical Effects:

SUMMARY OF EXPOSURE

- Most exposures to capsaicin come from handling peppers or paprika.
- Capsaicin is a chemical/irritant found in many plant species, belonging to the genus Capsicum, and can cause dermatitis as well as adverse nasal, pulmonary and gastrointestinal effects in humans.
- The oleoresin of capsicum is a major ingredient of "pepper gas" - personal protection weapons carried by many civilians and law enforcement personnel. These weapons can provide temporary immobilization of an assailant when sprayed into the face, especially the eyes. The "pepper gases" can contain C.S. (tear gas) or oleoresin of capsicum, or both.

HEENT
- Capsaicin is a mucous membranes irritant and will cause irritation of eyes, nose, and the lining of the mouth.

RESPIRATORY
- Capsaicin vapors, especially from burning, may cause significant pulmonary irritation and prolonged cough. Pulmonary edema and bronchospasm may occur.

NEUROLOGIC
- Stimulates pain fibers and release immunoreactive somatostatin.

GASTROINTESTINAL
- Biting plants which contain capsaicin may cause acute stinging of the lips, tongue, and oral mucosa, which may lead to vomiting and diarrhea. Epithelial cell sloughing or mild mucosal bleeding may occur.

HEMATOLOGIC
- Chronic ingestion may cause changes in coagulation parameters; platelet aggregation inhibition has been demonstrated.

DERMATOLOGIC
- Irritation, erythema, and burning pain without vesiculation often occurs when applied topically to human skin. Blistering and rash may occur after chronic or prolonged exposure.

ENDOCRINE
- Human data on glucose levels or metabolism is unclear. Animal data suggest possible hypoglycemia.

Laboratory:

- No toxic serum levels have been established.

Treatment Overview:

ORAL/PARENTERAL EXPOSURE
- EMESIS - Capsaicin's natural irritation may produce emesis.
- DILUTION: Immediately dilute with 4 to 8 ounces (120 to 240 mL) of milk or water (not to exceed 15 mL/kg in a child).
- ACTIVATED CHARCOAL: Administer charcoal as slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.

INHALATION EXPOSURE
- DECONTAMINATION: Move patient to fresh air. Monitor for respiratory distress. If cough or difficulty in breathing develops, evaluate for respiratory tract irritation, bronchitis, or pneumonitis. Administer 100

percent humidified supplemental oxygen with assisted ventilation as required.

EYE EXPOSURE

- DECONTAMINATION: Exposed eyes should be irrigated with copious amounts of tepid water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist, the patient should be seen in a health care facility.

DERMAL EXPOSURE

- Treatment is directed at thorough decontamination and relief of the pain at the site of the exposure.
- DECONTAMINATION: Wash exposed area extremely thoroughly with soap and water. A physician may need to examine the area if irritation or pain persists.
- Cold water has been recommended but seldom provides long lasting relief.
- Vinegar water irrigation has been touted as producing relief but has only been moderately successful.
- EMLA, an emulsion of lidocaine and prilocaine, may be used to treat skin that has been severely irritated by capsaicin. Relief from pain occurs approximately one hour after application of this mixture.
- Vegetable oil has been tested, and does provide a better long term relief from the pain of "chile burns."
- An antacid suspension containing magnesium and aluminum hydroxide, applied topically, has been reported to provide immediate pain relief following dermal exposure to pepper-mace sprays containing capsaicin.

Range of Toxicity:

- Concentrations of less than 10 (-4) molar will cause a burning sensation when applied to the tongue.
- Meals containing red pepper (0.1 to 1.5 g) or black pepper (1.5 g) will cause a significant increase in parietal secretion, pepsin secretion, and potassium loss.
- Application of capsaicin (75 mcg) into the human nasal mucosa will be followed by a burning sensation and sneezes, accompanied by the production of seromucous nasal secretion.

[Rumack BH: POISINDEX(R) Information System. Micromedex, Inc., Englewood, CO, 2001; CCIS Volume 107, edition exp February, 2001. Hall AH & Rumack BH (Eds):TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 2001; CCIS Volume 107, edition exp February, 2001.] **PEER REVIEWED**

Animal Toxicity Studies:

Non-Human Toxicity Excerpts:

... Fifty ug/ml /on the eyes of rats/ has caused obvious pain and blepharospasm. The blood vessels of the conjunctivae and lids became abnormally permeable to Evans blue dye injected intravenously. Application of local anesthetic prevented pain, but did not alter the vascular reaction.
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986. 175]**PEER REVIEWED**

GUINEA PIGS WERE MOST SUSCEPTIBLE SPECIES WITH LD50 OF 1.10 MG/KG WHEREAS HAMSTERS & RABBITS WERE LESS SUSCEPTIBLE. PROBABLE CAUSE OF DEATH

RESPIRATORY PARALYSIS.
[GLINSUKON ET AL; TOXICON 18 (2): 215 (1980)]**PEER REVIEWED**

HOWEVER, THERE WAS AN UPPER LIMIT TO THE RISE IN BODY TEMP IN BOTH GROUPS.
[SZ'EKELY M, SZOLCS'ANYI J; ACTA PHYSIOL ACAD SCI HUNG 53 (4): 469 (1979)]**PEER REVIEWED**

NEONATAL ADMIN DID NOT AFFECT MORPHINE. NEONATAL ADMIN CAUSED SELECTIVE DEGENERATION OF CHEMOSENSITIVE PRIMARY SENSORY NEURONS.
[JANCSO G, JANCSO-GABOR A; NAUNYN-SCHMIEDEBERG'S ARCH PHARMACOL 311 (3): 285 (1980)]**PEER REVIEWED**

PRETREATMENT OF ADULT RATS WITH CAPSAICIN INCR ANALGESIC EFFECT OF MORPHINE BUT NOT NEONATAL ADMIN (2 DAYS OR 2-3 MO OLD). HYPOTHALAMIC PREOPTIC REGION MAY BE IMPORTANT LINK IN PAIN CONTROLLING SYSTEM SINCE THIS IS REGION AFFECTED IN ADULTS.
[JANCSO G, JANCSO-GABOR A; NAUNYN-SCHMIEDEBERG'S ARCH PHARMACOL 311 (3): 285 (1980)]**PEER REVIEWED**

5 MG/KG IP TO RATS FOR 5 DAYS INCR MICROSOMAL CYTOCHROME P450 & NADPH-CYTOCHROME C REDUCTASE BY 14.6 & 11.6%, RESPECTIVELY. IT DECR HEXOBARBITAL SLEEP TIME, ZOXAZOLAMINE PARALYSIS TIME, & PLASMA HEXOBARBITAL LEVELS. IT APPEARS TO INDUCE DRUG-METABOLIZING ENZYMES IN LIVER.
[KIM ET AL; YAKHAK HOE CHI 23(2) 118 (1979)]**PEER REVIEWED**

SOME USE IRRITANT PEPPER ALKALOID, CAPSAICIN.../AS SPRAY DEFENSE AGAINST DOGS/ 7 DAILY APPLICATIONS PRODUCE METAPLASTIC CONJUNCTIVAL CHANGES, WHICH ARE RESOLVED A MO AFTER LAST APPLICATION.
[Rossoff, I.S. Handbook of Veterinary Drugs. New York: Springer Publishing Company, 1974. 76]**PEER REVIEWED**

There is some concern that capsaicin may be potentially neurotoxic, although animal ... studies with topical capsaicin have not shown this to occur.
[USP Convention. USPDI-Drug Information for the Health Care Professional. 14th ed. Volume I. Rockville, MD: United States Pharmacopeial Convention, Inc., 1994. (Plus Updates). 710]**PEER REVIEWED**

In the Draize Test, capsaicin was neither an eye or primary skin irritant in the rabbit, but was irritating to the dog's eye. Local capsaicin in the rat's eye caused low density of microvesicles and swollen mitochondria in nerve endings in the cornea, but no signs of axonal degeneration or alteration in fine structure of non-neural elements. Capsaicin prevents degranulation of skin mast cells induced by topical benzene or antidromic stimulation of cutaneous nerve in the rat. Pretreatment with capsaicin prevented leakage of Evan's blue into the rat's skin treated with skin irritants. Capsaicin produced a reversible decrease in the membrane potential of the isolated frog skin in vitro. The rat duodenal tissue exposed to capsaicin showed swollen mitochondria with rarified matrix and disorganized cristae, there was an increased number of free ribosomes, and lysosomes and dilatation of endoplasmic reticulum and Golgi complexes, nuclei were shrunken and chromatin was clumped and marginated at the nuclear envelope. This drug produces prolonged desensitization of peripheral nerve endings.
[Sax, N.I. Dangerous Properties of Industrial Materials. 6th ed. New York, NY: Van Nostrand Reinhold, 1984. 629]**PEER REVIEWED**

Intravitreal injection of capsaicin in rabbits causes miosis and breakdown of the blood-aqueous barrier. This response can be blocked by pretreatment with tetrodotoxin or a "substance P" antagonist.

[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986. 176]**PEER REVIEWED**

When given systemically to rodents, ... /capsaicin/ temporarily blocks their nociceptive sensory nerves, probably by depleting them of substance P. The eyes of animals pretreated in this manner do not react normally to painful chemical stimuli, such as topical nitrogen mustard, or intracameral formaldehyde or capsaicin. These eyes do not develop miosis, hyperemia of the iris, or elevation of intraocular pressure in the way the eyes of untreated animals do.
[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986. 176]**PEER REVIEWED**

Capsaicin was administered in a semisynthetic powdered diet at 0.03125% level for the lifespan of Swiss mice starting from 6 weeks of age. As a result of C treatment, tumors of the cecum were induced in 22% of females and 14% of males, whereas the corresponding tumor incidences in untreated female and male controls were both 8%. Histopathologically, the tumors were classified as benign polypoid adenomas.
[Toth B, Gannett P; In Vivo 6 (1): 59-63 (1992)]**PEER REVIEWED**

Previous results indicate that the pattern of capsaicin-induced degeneration in the rat central nervous system is age related. Experiments utilizing capsaicin's selective neurodegenerative effects to study the function of central neural circuits will therefore require a detailed understanding of capsaicin's central neurotoxicity in rats of different ages. The goal of this experiment was to characterize the degeneration induced in the rat brain by systemic treatment with capsaicin at different ages (10, 15, 20, 25, 30 or 75 days, or 11 months), using a cupric silver stain to label degenerating neurons. Results revealed degenerating cell bodies in the ventromedial brainstem in capsaicin-treated rats of all age groups though they were more numerous in adult rats than in pups. In addition many areas contained capsaicin-induced nerve terminal degeneration both in rat pups and in adult rats. These areas were the substantia gelatinosa of the spinal cord dorsal horn; the solitary tract; the nucleus of the solitary tract, visceral portion; the area postrema; the trigeminal nerve and spinal trigeminal nucleus; the medial nucleus of the inferior olive; the rostral dorsomedial and dorsolateral interpeduncular subnuclei and overlying interfascicular nucleus; the supramammillary area; the lateral septal nucleus; the bed nucleus of the stria terminalis anterior medial portion; the optic nerve and tract; the suprachiasmatic nucleus ventroposterolateral portion; the magnocellular subnucleus of the ventrolateral geniculate nucleus; the intergeniculate leaf; the medial pretectal nucleus and the olivary pretectal nucleus. In several but not all of these areas the apparent density of degenerating terminals was significantly less in adult rats than in pups. In other brain sites capsaicin-induced degeneration was observed only in rats younger than 30 days of age. These areas were the lateral habenula medial part; the sphenoid nucleus; and the stria medullaris. Still other brain sites lost their sensitivity to capsaicin sometime between 30 and 75 days of age. These areas were the bed nucleus of the stria terminalis medial posteromedial part; the medial preoptic nucleus central part; the septohypothalamic nucleus; the ventral reuniens area; and the ventromedial hypothalamic nucleus. Adult rats 75 days and 11 months of age did not differ detectably in their response to capsaicin. Thus, loss or attenuation of capsaicin sensitivity is not progressive throughout life. It does not occur in all capsaicin-sensitive sites. Where it does occur loss of sensitivity occurs prior to adulthood and follows a distinct and reproducible time course that may differ for different sites.
[Ritter S, Dinh TT; J Comp Neurol 318 (1): 103-16 (1992)]**PEER REVIEWED**

Capsaicin has been used extensively as an experimental tool and in traditional and proprietary topical medications for acute soft tissue injuries. More recently it has been prescribed for several chronic pain conditions where it is usually administered topically for periods of several weeks. ... The consequences of this mode of application /have been studied/ in the rat. Capsaicin cream (0.075% or 0.75%) or a vehicle cream was applied twice daily to the hind paws of rats for a continuous period of 10 weeks. The hind paws treated with 0.75% capsaicin (but not 0.075%) became transiently hyperalgesic but there were

no signs of discomfort or distress associated with the treatment. After 10 weeks of capsaicin application the ability of C fibers to produce neurogenic extravasation was markedly reduced. After 4 weeks of recovery this ability returned to normal in 0.075 capsaicin treated animals but remained impaired in the 0.75% group. This latter group showed a partial recovery 12 weeks after the end of treatment. The levels of substance P and CGRP in the sural nerve supplying the treated skin area were unchanged after both the 0.075% and 0.75% capsaicin treatments. The results suggest that the topical application of capsaicin at low concentration produces a reversible impairment of the terminals of C fibers in the skin without greatly exciting those fibers and without affecting the properties of cell soma. The number of afferent neurons in the L5 dorsal root ganglion projecting through the sural nerve was unchanged after 0.75% capsaicin treatment suggesting that the topical capsaicin treatment does not produce any cell death in the adult animal.
[McMahon SB et al; Pain 44 (3): 301-10 (1991)]**PEER REVIEWED**

In L3 and L4 dorsal roots 85-93% of unmyelinated fibers and 9-33% of myelinated fibers were lost after 50-100 mg/kg capsaicin in neonatal rats. In rats treated with 85 mg/kg capsaicin, percentage losses of unmyelinated (89%) and myelinated (36%) fibers of L4 dorsal roots were remarkably similar to the calculated losses of small dark (92%) and large light (34%) neurones respectively in these ganglia. Studies with monoclonal antibody RT97 which labels the large light neurones only, confirmed that some RT97 negative cells (ie small dark neurones) remain after capsaicin treatment. At present no evidence exists to suggest that the cell death of small dark neurones or C fibers after neonatal capsaicin treatment is completely selective for subgroups of these neurones, either in relation to sensory modality, or in relation to immunocytochemical cell markers and peptide content. However much more data is required to establish whether this cell death is really nonselective as regards immunocytochemical markers.
[Lawson SN; Acta Physiol Hung 69 (3-4): 315-21 (1987)]**PEER REVIEWED**

Metabolism/Pharmacokinetics:

Mechanism of Action:

Capsaicin reduces ... pain ... by interfering with substance P-mediated pain transmission. ... Capsaicin may decrease the sensitivity by depleting and inhibiting the reuptake of substance P in the peripheral neuron.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994. 148]**PEER REVIEWED**

Capsaicin, the pungent constituent of chili peppers, represents the paradigm for the capsaicinoids or vanilloids, a family of compounds shown to stimulate and then desensitize specific subpopulations of sensory receptors, including C-polymodal nociceptors, A-delta mechanoheat nociceptors and warm receptors of the skin, as well as enteroceptors of thin afferent fibers. An exciting recent advance in the field has been the finding that resiniferatoxin (RTX), a naturally occurring diterpene containing a homovanillic acid ester, a key structural motif of capsaicin, functions as an ultrapotent capsaicin analog. For most of the responses characteristic of capsaicin, RTX is 100-10,000 fold more potent. Structure/activity analysis indicates, however, that RTX and related homovanillyl-diterpene esters display distinct spectra of activity. Specific (3H)RTX binding provides the first direct proof for the existence of vanilloid receptors. We expect that the RTX class of vanilloids will promote rapid progress in understanding of vanilloid structure/activity requirements and mechanism.
[Szallasi A, Blumberg PM; Life Sci 47 (16): 399-40 (1990)]**PEER REVIEWED**

Interactions:

Chemically-induced mutagenesis and carcinogenesis is modulated by various plant products, some of

which are present in the human diet. 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone, a potent carcinogen in tobacco and tobacco smoke, is activated by microsomal enzymes. In this study, we investigated the effects of capsaicin on the in vitro metabolism of 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone. Capsaicin is the principal component of Capsicum fruits used widely by humans as a food additive. Liver microsomes from saline-injected, phenobarbital-induced and beta-naphthoflavone-induced hamsters were used. Microsomes from phenobarbital and beta-naphthoflavone-induced animals expressed decreased 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone reduction and enhanced pyridine-N-oxidation, but did not significantly alter alpha-carbon hydroxylation of 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone. Capsaicin 10.5 mM) inhibited the formation of all metabolites of 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone by all microsomal fractions and inhibited alpha-hydroxylation by phenobarbital-induced microsomes more than by either of the other two treatments. Our results suggest that capsaicin, as a naturally occurring dietary constituent, possesses antimutagenic and anticarcinogenic properties through the inhibition of xenobiotic metabolizing enzymes.
[Miller CH et al; Cancer Lett 75 (1): 45-52 (1993)]**PEER REVIEWED**

To examine whether blockade of chemosensitivity of corneal nociceptors by Ca2+ antagonists decreases pain and irritation induced by capsaicin. In adult rabbits the number of lid-squeezing movements and the degree of palpebral opening miotic response and conjunctival vasodilation evoked by a bilateral instillation of 30 ul of capsaicin (33 mM) were measured at different times (up to 5 hr) after the drug. Irritative responses to capsaicin in eyes pretreated with diltiazem verapamil, or nifedipine were compared with those that received only the vehicle. Protein content in aqueous humor was also measured at the end of the experiment. Diltiazem at doses of 1 to 28 mM administered 15 minutes before the application of capsaicin significantly decreased scratching movements conjunctival hyperemia closure of the eye and elevated aqueous protein concentration induced by capsaicin; however it did not significantly reduce miosis. Nifedipine (2.8 and 10 mM) diminished the number of scratching movements but not other inflammatory parameters, whereas verapamil (2.8 and 10 mM) was totally ineffective in attenuating ocular signs of irritation produced by capsaicin. These results suggest that by lowering capsaicin-induced neural activity in nociceptive terminals diltiazem decreases pain and neurogenic inflammation and may be useful as both an analgesic and an antiinflammatory agent in the eye.
[Gonzalez GG et al; Investigative Ophthalmology & Visual Science 34 (12): 3329-35 (1993)]**PEER REVIEWED**

Pharmacology:

Therapeutic Uses:

Capsaicin reduces the pain of posttherpetic neuralgia and diabetic neuropathy ... A topical application of capsaicin 0.025% for four to six weeks has been shown to provide either complete or significant relief of chronic posttherpetic pain. ... Initial results of a multicenter controlled trial with topical capsaicin cream 0.075% suggest that this preparation produced more relief of the pain associated with diabetic neuropathy than placebo. Approximately 75% of patients claimed pain relief from capsaicin compared with 45% of patients treated with cream containing the vehicle only; however, a significant difference was noted only after four weeks of treatment.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994. 148]**PEER REVIEWED**

Capsaicin is indicated for the treatment of neuralgias, such as the pain following herpes zoster (shingles) and painful diabetic neuropathy; osteoarthritis; or for the treatment of pain from osteoarthritis and rheumatoid arthritis.
[USP Convention. USPDI-Drug Information for the Health Care Professional. 14th ed.

Volume I. Rockville, MD: United States Pharmacopeial Convention, Inc., 1994. (Plus Updates). 710]**PEER REVIEWED**

Capsaicin is used to treat the pain associated with postmastectomy pain syndrome and reflex sympathetic dystrophy syndrome. /Not included in US product labeling/
[USP Convention. USPDI-Drug Information for the Health Care Professional. 14th ed. Volume I. Rockville, MD: United States Pharmacopeial Convention, Inc., 1994. (Plus Updates). 710]**PEER REVIEWED**

Capsaicin is approved for the relief of pain that follows herpes zoster infections (postherpetic neuralgia).

[Gilman, A.G., T.W. Rall, A.S. Nies and P. Taylor (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, NY. Pergamon Press, 1990. 1587]**PEER REVIEWED**

Capsaicin is available as a 0.025% cream (Zostrix), which is applied three to four times per day to the affected skin after open lesions have healed. The only toxicity noted is occasional local burning.
[Gilman, A.G., T.W. Rall, A.S. Nies and P. Taylor (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, NY. Pergamon Press, 1990. 1587]**PEER REVIEWED**

A large double blind vehicle-controlled study of 143 patients with chronic postherpetic neuralgia was performed to evaluate the degree of efficacy of topically applied capsaicin 0.075% cream. In addition the safety and efficacy of long-term application of topical capsaicin In postherpetic neuralgia was assessed by following patients in an open-label study for up to 2 years. In the double-blind phase 143 patients with postherpetic neuralgia of 6 months duration or longer were enrolled. Since epidemiologic studies of patients who receive no treatment have shown that only 10% to 25% of those with postherpetic neuralgia after 1 month will still have pain at 1 year two separate efficacy analyses were performed: one with all evaluable patients (n = 131) and the other with 93 patients whose postherpetic neuralgia lasted for longer than 12 months prior to study startup. All efficacy variables including the physicians global evaluation of reduction in postherpetic neuralgia pain changes in pain severity on the categoric scale visual analog scale for pain severity visual analog scale for pain relief and functional capacity scale showed significant improvement at nearly all time points throughout the study for both patient groups based on duration of postherpetic neuralgia pain. In contrast the group receiving vehicle cream remained essentially unchanged. Data from the long-tern open-label phase (up to 2 years n = 77), which immediately followed the 6 week blinded phase showed that the clinical benefit in patients treated for a short (6 week) period with topical capsaicin could be maintained or amplified in most patients (86%) during prolonged therapy. There were no serious adverse effects observed or reported throughout the trial; in fact the only side effect associated with capsaicin treatment was the burning or stinging at local sites of application (in 9% of patients) during exposures of up to 2 years (long-term phase). The basis of these data we conclude that capsaicin 0.075% cream is a safe and effective treatment for the pain of postherpotic neuralgia and should be considered for initlal management of patients with this condition.
[Watson CP et al; Clin Ther 15 (3): 510-26 (1993)]**PEER REVIEWED**

Drug Warnings:

A mild to moderate burning sensation is experienced following application and, in some patients, can be pronounced enough to require discontinuation of treatment.
[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994. 148]**PEER REVIEWED**

/Capsaicin must be prevented/ from entering the eyes, open lesions, or mucous membranes.

[American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994. 148]**PEER REVIEWED**

Patients may experience a warm, stinging, or burning sensation at the site of application, especially during the initial few days of use. Although this sensation frequently disappears after the first several days of treatment, it may persist for 2 to 4 weeks or longer. This effect is related to the initial excitatory effect of capsaicin on the C fibers and their release of substance P. The burning usually decreases in frequency and intensity with the continued administration of capsaicin. However, application schedules of capsaicin of less than 3 or 4 times daily may prolong the burning sensation while not providing optimum pain relief. Environmental factors, such as heat or humidity; wrappings, such as clothing or bandages; bathing in warm water; or sweating may intensify the sensation. The incidence of the burning sensation has been variable in difference studies. This may be related to the etiology and pathogenesis of the pain syndrome in different persons. For example, patients with arthritis generally experience less intense burning than do patients with peripheral neuropathies.
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If using capsaicin for treatment of neuralgia due to herpes zoster, /do/ not apply medicine until after zoster sores have healed.
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Interactions:

Chemically-induced mutagenesis and carcinogenesis is modulated by various plant products, some of which are present in the human diet. 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone, a potent carcinogen in tobacco and tobacco smoke, is activated by microsomal enzymes. In this study, we investigated the effects of capsaicin on the in vitro metabolism of 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone. Capsaicin is the principal component of Capsicum fruits used widely by humans as a food additive. Liver microsomes from saline-injected, phenobarbital-induced and beta-naphthoflavone-induced hamsters were used. Microsomes from phenobarbital and beta-naphthoflavone-induced animals expressed decreased 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone reduction and enhanced pyridine-N-oxidation, but did not significantly alter alpha-carbon hydroxylation of 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone. Capsaicin 10.5 mM) inhibited the formation of all metabolites of 4-(methylnitrosamino)-1-13-pyridyl)-1-butanone by all microsomal fractions and inhibited alpha-hydroxylation by phenobarbital-induced microsomes more than by either of the other two treatments. Our results suggest that capsaicin, as a naturally occurring dietary constituent, possesses antimutagenic and anticarcinogenic properties through the inhibition of xenobiotic metabolizing enzymes.
[Miller CH et al; Cancer Lett 75 (1): 45-52 (1993)]**PEER REVIEWED**

To examine whether blockade of chemosensitivity of corneal nociceptors by Ca2+ antagonists decreases pain and irritation induced by capsaicin. In adult rabbits the number of lid-squeezing movements and the degree of palpebral opening miotic response and conjunctival vasodilation evoked by a bilateral instillation of 30 ul of capsaicin (33 mM) were measured at different times (up to 5 hr) after the drug. Irritative responses to capsaicin in eyes pretreated with diltiazem verapamil, or nifedipine were compared with those that received only the vehicle. Protein content in aqueous humor was also measured at the end of the experiment. Diltiazem at doses of l to 28 mM administered 15 minutes before the application of capsaicin significantly decreased scratching movements conjunctival hyperemia closure of the eye and elevated aqueous protein concentration induced by capsaicin; however it did not significantly reduce miosis. Nifedipine (2.8 and l0 mM) diminished the number of scratching

movements but not other inflammatory parameters, whereas verapamil (2.8 and 10 mM) was totally ineffective in attenuating ocular signs of irritation produced by capsaicin. These results suggest that by lowering capsaicin-induced neural activity in nociceptive terminals diltiazem decreases pain and neurogenic inflammation and may be useful as both an analgesic and an antiinflammatory agent in the eye.
[Gonzalez GG et al; Investigative Ophthalmology & Visual Science 34 (12): 3329-35 (1993)]**PEER REVIEWED**

Minimum Fatal Dose Level:

3(?). 3= MODERATELY TOXIC: PROBABLE ORAL LETHAL DOSE (HUMAN) 0.5-5 G/KG, BETWEEN 1 OZ & 1 PINT (OR 1 LB) FOR 70 KG PERSON. /CAPSICUM/
[Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976.,p. II-145] **PEER REVIEWED**

Environmental Fate & Exposure:

Natural Pollution Sources:

Capsaicin is a naturally occurring substance in plants of the Solanaceae family.
[USP Convention. USPDI-Drug Information for the Health Care Professional. 14th ed. Volume I. Rockville, MD: United States Pharmacopeial Convention, Inc., 1994. (Plus Updates). 710]**PEER REVIEWED**

Environmental Standards & Regulations:

FIFRA Requirements:

As the federal pesticide law FIFRA directs, EPA is conducting a comprehensive review of older pesticides to consider their health and environmental effects and make decisions about their future use. Under this pesticide reregistration program, EPA examines health and safety data for pesticide active ingredients initially registered before November 1, 1984, and determines whether they are eligible for reregistration. In addition, all pesticides must meet the new safety standard of the Food Quality Protection Act of 1996. Pesticides for which EPA had not issued Registration Standards prior to the effective date of FIFRA, as amended in 1988, were divided into three lists based upon their potential for human exposure and other factors, with List B containing pesticides of greater concern and List D pesticides of less concern. Capsaicin is found on List D. Case No: 4018; Pesticide type: insecticide, vertebrate repellent; Case Status: RED Approved 09/91; OPP has made a decision that some/all uses of the pesticide are eligible for reregistration, as reflected in a Reregistration Eligibility Decision (RED) document.; Active ingredient (AI): Capsaicin (in oleoresin of capsicum); AI Status: OPP has completed a Reregistration Eligibility Decision (RED) document for the case/AI.
[USEPA/OPP; Status of Pesticides in Registration, Reregistration and Special Review p.___ (Spring, 1998) EPA 738-R-98-002]**QC REVIEWED**

Chemical/Physical Properties:

Molecular Formula:

C18-H27-N-O3
PEER REVIEWED

Molecular Weight:

305.42
PEER REVIEWED

Color/Form:

MONOCLINIC, RECTANGULAR PLATES, SCALES FROM PETROLEUM ETHER
[Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989.,p. 266-267]**PEER REVIEWED**

Taste:

BURNING
[Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989.,p. 266-267]**PEER REVIEWED**

Boiling Point:

210-220 DEG C @ 0.01 MM HG
[Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989.,p. 266-267]**PEER REVIEWED**

Melting Point:

65 DEG C
[Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989.,p. 266-267]**PEER REVIEWED**

Octanol/Water Partition Coefficient:

Log Kow = 3.04
[LaHann TR et al; Proc West Pharmacol Soc 32: 201-4 (1989)]**PEER REVIEWED**

Solubilities:

PRACTICALLY INSOL IN COLD WATER; FREELY SOL IN ALCOHOL, ETHER, BENZENE, CHLOROFORM; SLIGHTLY SOL IN CARBON DISULFIDE
[Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989.,p. 266-267]**PEER REVIEWED**

SLIGHTLY SOL IN CONCENTRATED HYDROCHLORIC ACID
[Weast, R.C. (ed.). Handbook of Chemistry and Physics. 60th ed. Boca Raton, Florida: CRC Press Inc., 1979.,p. C-237]**PEER REVIEWED**

Soluble in petroleum ether
[Lide, DR (ed.). CRC Handbook of Chemistry and Physics. 71st ed. Boca Raton, FL: CRC Press Inc., 1990-1991.,p. 2\3-164]**PEER REVIEWED**

Spectral Properties:

MAX ABSORPTION (ALCOHOL): 227 NM (LOG E= 3.91); 281 NM (LOG E= 3.43)

[Weast, R.C. (ed.). Handbook of Chemistry and Physics. 60th ed. Boca Raton, Florida: CRC Press Inc., 1979.,p. C-237]**PEER REVIEWED**

IR: 17226 (Sadtler Research Laboratories IR Grating Collection)
[Weast, R.C. and M.J. Astle. CRC Handbook of Data on Organic Compounds. Volumes I and II. Boca Raton, FL: CRC Press Inc. 1985.,p. V1 394]**PEER REVIEWED**

UV: 2-581 (Organic Electronic Spectral Data, Phillips et al, John Wiley & Sons, New York)
[Weast, R.C. and M.J. Astle. CRC Handbook of Data on Organic Compounds. Volumes I and II. Boca Raton, FL: CRC Press Inc. 1985.,p. V1 394]**PEER REVIEWED**

UV max: 227, 281 nm (E 7000, 2500)
[Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989.,p. 266-267]**PEER REVIEWED**

Chemical Safety & Handling:

Skin, Eye and Respiratory Irritations:

Contact with products containing capsaicin produces local irritation and lacrimation.
[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988. 1239] **PEER REVIEWED**

Disposal Methods:

SRP: At the time of review, criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision. Prior to implementing land disposal of waste residue (including waste sludge), consult with environmental regulatory agencies for guidance on acceptable disposal practices.
PEER REVIEWED

Occupational Exposure Standards:

Manufacturing/Use Information:

Major Uses:

FLAVORING AGENT IN FOODS
[SRI]**QC REVIEWED**

MEDICATION
QC REVIEWED

Manufacturers:

NOT PRODUCED COMMERCIALLY IN THE US
[SRI]**PEER REVIEWED**

Methods of Manufacturing:

REACTION OF VANILLYLAMINE WITH 7-METHYLOCT-5-ENE-1-CARBOXYLIC ACID CHLORIDE; BIOSYNTHESIS FROM CAPSICUM FRUTESCENS (RED PEPPERS)

[SRI]**PEER REVIEWED**

PUNGENT PRINCIPLE IN FRUIT OF VARIOUS SPECIES OF CAPSICUM, SOLANACEAE. ISOLATION FROM PAPRIKA AND CAYENNE.
[The Merck Index. 9th ed. Rahway, New Jersey: Merck & Co., Inc., 1976. 224]**PEER REVIEWED**

U. S. Production:

(1977) NOT PRODUCED COMMERCIALLY IN USA
[SRI]**PEER REVIEWED**

(1979) NOT PRODUCED COMMERCIALLY IN USA
[SRI]**PEER REVIEWED**

Laboratory Methods:

Analytic Laboratory Methods:

CAPSAICIN WAS EXTRACTED FROM OINTMENTS CONTAINING 20% CAPSICUM ANNUUM EXTRACT. CAPSAICIN WAS DETERMINED BY COLOR REACTION WITH PHOSPHOMOLYBDIC ACID, READ AT 762 NM. CONTENT OF 7 SAMPLES WAS 0.2 +- 0.01%.
[TOMOVA ET AL; PHARMAZIE 34 (7): 448 (1979)]**PEER REVIEWED**

GC DETERMINATION OF CAPSAICINE IN FRUCTUS CAPSICI.
[JURENITSCH ET AL; SCI PHARM 46 (4): 307 (1978)]**PEER REVIEWED**

HPLC DETERMINATION OF CAPSAICINE IN CAPSAICINOID MIXTURES AND IN FRUCTUS CAPSICI.
[STICHER ET AL; J CHROMATOGR 166 (1): 221 (1978)]**PEER REVIEWED**

Special References:

Synonyms and Identifiers:

Synonyms:

N-(4-HYDROXY-3-METHOXYBENZYL-8-METHYLNON-TRANS-6-ENAMIDE
PEER REVIEWED

(E)-N-[(4-HYDROXY-3-METHOXYPHENYL)-METHYL]-8-METHYL-6-NONENAMIDE
PEER REVIEWED

TRANS-8-METHYL-N-VANILLYL-6-NONENAMIDE
PEER REVIEWED

6-NONENAMIDE, N-((4-HYDROXY-3-METHOXYPHENYL)METHYL)-8-METHYL-, (E)-
PEER REVIEWED

6-NONENAMIDE, 8-METHYL-N-VANILLYL-, (E)-
PEER REVIEWED

STYPTYSAT
PEER REVIEWED

RTECS Number:

NIOSH/RA8530000

Administrative Information:

Hazardous Substances Databank Number: 954

Last Revision Date: 20000912

Last Review Date: Reviewed by SRP on 9/29/1994

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Complete Update on 12/20/1984

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